

**United States Patent** [19]  
**Mayer et al.**

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[54] **INHIBITING THE DEVELOPMENT OF  
TOLERANCE TO AND/OR DEPENDENCE ON  
AN ADDICTIVE SUBSTANCE**

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[\*] **Notice:** The term of this patent shall not extend  
beyond the expiration date of Pat. No.  
5,321,012.

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**Related U.S. Application Data**

[63] Continuation of Ser. No. 43,280, Apr. 6, 1993, Pat. No.  
5,321,012, which is a continuation-in-part of Ser. No.  
10,583, Jan. 28, 1993, abandoned.

[51] **Int. Cl.<sup>6</sup>** ..... **A61K 31/70; A61K 31/54;  
A61K 31/44; A61K 31/445**

[52] **U.S. Cl.** ..... **514/25; 514/216; 514/223.5;  
514/225.5; 514/224.5; 514/282; 514/231.2;  
514/304; 514/305; 514/306; 514/307; 514/812**

[58] **Field of Search** ..... **514/25, 304, 305,  
514/306, 307, 216, 223.5, 225.5, 224.5,  
282, 231.2, 812**

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[57] **ABSTRACT**

Nontoxic substances that block the N-methyl-D-aspartate  
(NMDA) receptor, e.g., a morphinan such as dextrometho-  
rphan or dextrorphan, or that block a major intracellular  
consequence of NMDA-receptor activation, e.g., a ganglio-  
side such as GM<sub>1</sub> or GT<sub>1b</sub>, a phenothiazine such as triflu-  
operazine or a naphthalenesulfonamide such as N-(6-ami-  
nohexyl)-5-chloro-1-naphthalenesulfonamide, inhibit the  
development of tolerance to and/or dependence on addictive  
drugs, e.g., narcotic analgesics such as morphine, codeine,  
etc.

**2 Claims, 10 Drawing Sheets**